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Case report

KETOTIC HYPOGLYCEMIA IN CHILDREN "NOT AN UNCOMMON ENTITY BUT IS RARELY THOUGHT OF": CASE SERIES

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ABSTRACT

Ketotic hypoglycemia is the most common form of childhood hypoglycemia. Periods of Hypoglycemic episodes typically occur during early morning, especially during intercurrent illness when food intake is limited. The symptoms and signs of hypoglycemia are often overlooked .Because hypoglycemia is a life threatening event can lead to severe neurological sequel, intravenous administration of glucose is necessary. These children respond promptly to glucose. We share our experience of four cases of Ketotic hypoglycemia admitted during last 2 years.

Key words: Hypoglycemia, Ketosis, Ketotic hypoglycemia, Methylcrotonyl-CoAcarboxylase.

INTRODUCTION

Ketotic hypoglycemia (KH) is a good example of 'what eyes don't see that mind doesn't know'. KH should be suspected in every child who present with early morning drowsiness and/ or convulsions especially after poor intake on the previous day. So any child presenting with such symptoms and hypoglycemia proved by glucometer, urine should be immediately sent for ketone bodies. If urine ketones are positive the most likely cause is KH.[1]

With such an approach we were able to detect more cases of Ketotic hypoglycemia during the last few months. This has now become a routine PICU protocol for children presenting with morning seizures, drowsiness altered sensorium. Blood glucose estimation and urine for ketone bodies as a bedside test are done and confirmed by laboratory. It is considered as a benign condition as neurological damage and other sequels are rare [2]. The inform consent taken from parents in the study.

CASE SERIES

Case1. A 6 years old female presented with complaints of early morning generalized tonic-clonic convulsions. She had similar episodes 6 times in the past; all occurred early in the morning. She had been diagnosed as epilepsy and had been put on anticonvulsants. Seizure episodes continued. Each episode was associated with skipping dinner the previous night.

Case2. A 7 years old female presented with drowsiness since morning, difficulty in arousing her from sleep and mild grade fever since one day. History of skipped dinner the previous night. There was a past history of similar episode 3 months ago. She had been admitted in private hospital we had low blood sugar was documented. She improved with IV dextrose and was discharged. Ketotic hypoglycemia was neither thought of nor investigated during the previous episode. We also documented marked hypoglycemia during this episode.

Case 3. A 4 years male came with the history of loose motions since previous evening and history of poor oral intake since previous afternoon. The child has been drowsy since morning. There were no signs of dehydration. No history of convulsions.

Case 4. A 2 ½ years old female admitted with altered sensorium and generalized tonic-clonic convulsions early in the morning. There was no history of fever.

As per protocols blood sugar was obtained in all the patients, who showed severe hypoglycemia in the range of 20- 35mg/dl on glucometer (Model no.Abbott 0088,Abbott Diabetes care ltd, ART 16648,Rev.B05/10) Hypoglycemia was confirmed by laboratory method (Glucose Oxidase Peroxidase) also. Urine ketones were positive in all patients 3+ to 4+,

Anthropometry, general and systemic examination was normal in all cases. Biochemical parameters like serum calcium, serum magnesium, Liver function test, Renal function test, Ceribro spinal fluid, CT scan head and EEG done in all patients, were within normal limits.

All the four cases were managed according to routine emergency management. IV 10 % dextrose bolus was given, followed by appropriate IV fluid infusion. Blood glucose level was monitored until condition was stabilized.

Out of four, only three patients case 1,2,3 were investigated for metabolic disorders by tandem mass spectrometry (TMS) due to financial constraints these could not be done in case 4. Reports of case1,3 patients were within normal limits.

TMS report of one patient case 2 came positive for acylcarnitine profile showing increased levels of 3-OH isovalerylcarnitine (C5OH). Urinary organic acid profile showed increased levels of 3-methylcrotonyl glycine. Above findings were suggestive of inborn error of metabolism of leucine metabolism due to deficiency of enzyme 3-methylcrotonyl-CoA carboxylase (MCC)[3]. This child was kept on oral carnitine, restricted protein diet and asked for regular follow-up.

All patients were discharged with an advice of frequent feedings of a high-carbohydrate, balance protein diet and no skipping dinner at night especially during intercurrent illnesses. Parents were asked to monitor urine ketones during intercurrent illness by ketosticks. They were also told that an improvement and a marked reduction in the occurrence of these episodes can be expected as the child grows and attains puberty and adolescence, with an increase in muscle mass.

DISCUSSION

KH is most commonly seen in early childhood between 1.5-5years of age. Condition remits spontaneously by the age of 8–9 years. Hypoglycemic episodes typically occur during periods of intercurrent illness when food intake is limited. The classic history is of a child, who eats poorly or completely avoids the evening meal, who is difficult to arouse from sleep the following morning, and may have a seizure or be comatose by early or mid morning. Infants with this condition do not manifest hypoglycemia due to frequent breastfeeding.

The etiology of ketotic hypoglycemia may be a defect in any of the complex steps involved in protein catabolism, oxidative deamination of amino acids, transamination, alanine synthesis, or alanine efflux from muscle. Rarely, inborn errors of fatty acid metabolism present as ketotic hypoglycemia, although, typically, fatty acid

oxidation defects produce hypoketotic hypoglycemia[1]. Diet rich in Carbohydrates and Protein with more frequent feeding is the recommended treatment for ketotic hypoglycemia. The appearance of ketone in urine precedes hypoglycemia by several hours. Parents are advised to test the child's urine for the presence of ketones. In the presence of ketonuria, liquids of high carbohydrate content should be given. Patient requires hospitalization in case if oral feeding is not tolerated. During the intercurrent illness, if frequent estimations and early detection of urinary ketones done at home, hypoglycemia can be prevented (as ketones are detected in urine much before hypoglycemia).

Other causes of hypoglycemia with ketosis – Adrenal insufficiency, Hypopituitarism, Glucose-6-phosphatase debrancher defect, Fructose-1, 6-diphosphatase defect, Galactosemia, glycogen storage disease, fatty acid oxidation defects. Adrenal insufficiency, Hypopituitarism, glycogen storage disease, galactosemia could be the other cause in children and infants with seizures, drowinessor coma in the morning. Glucose-6-phosphatase debrancher defect, Fructose-1,6-diphosphatase defect have moderate hepatomegaly. Fatty acid oxidation defects usually do not manifest as ketosis. More advanced investigations like estimation serum levels of alanine, insulin, and lactate before and after deliberate fasting for 24-36 hours are not done in our cases due to non availability and economic reasons.

3-Methylcrotonyl-CoA Carboxylase (3-MCC) Deficiency: 3-Methylcrotonyl-CoA Carboxylase (3-MCC) deficiency has been recognized since 1984[7].It is a defect in the degradation of the amino acid leucine which is glucogenicaminoacid[7]. The clinical presentations of 3-MCC deficiency range from mild to severe illness. The age of onset of 3-Methylcrotonyl-CoA Carboxylase (3-MCC) deficiency symptoms is between 1-5 years. Clinical presentation is often with infection, illness, or after fasting. Most common symptoms are vomiting, lethargy, hypotonia, apnea, or hyperreflexia and seizures[8]. Patients may have profound hypoglycemia, mild metabolic acidosis, hyperammonemia, elevated liver transaminases, and ketonuria[8]. Plasma free carnitine may be low. Newborn Screening using tandem mass spectrometry reveals an elevation of C5-hydroxy acylcarnitine from the dried blood spot of an affected patient. Diagnosis of 3-MCC deficiency then requires further testing. Urine organic acid analysis finds elevation of 3- hydroxyisovaleric acid and usually 3-methylcrotonylglycine[3].

The condition is inherited as an autosomal recessive trait. The gene for α subunit (*MCC1*) is located on chromosome 3q25–27 and that for the β subunit (*MCC2*) is mapped to chromosome 5q12–13. Mutation in either of these genes may result in the deficiency of the enzyme activity[5]. Tandem mass spectrometry have identified an unexpectedly high number of infants with 3-methylcrotonyl CoA carboxylase deficiency (1:50,000), suggesting that this condition may be one of the most common organic acidemias in certain populations[4].

Assay of 3-MCC in fibroblasts or leukocytes can be used for confirmation of deficiency, along with at least one other carboxylase having normal enzyme activity must also be assayed.[3]This assay was not possible in our case.

CONCLUSION

KH though not uncommon, require a high index of suspicion and should be suspected in any child with early morning seizure, drowsiness and / or altered sensorium and confirmed by glucometer. Urinary ketones should be done routinely in such patients. Further metabolic screening and other advanced investigations may be done after inquiry of consanguinity, proper history and clinical examination. Early recognition of the condition will prevent further hypoglycemic episodes and unnecessary anticonvulsants. TMS should be done in every patient to find a rare metabolic disorder.

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